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Crohn's disease complicated by IgA vasculitis during tumor necrosis factor-α inhibitor therapy

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Short title: Crohn's disease and IgA vasculitis during TNF-α inhibitor therapy

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A 50-year-old man with a 26-year history of ileocolonic Crohn's disease (CD) presented with purpura and ankle joint pain. He had been treated with maintenance dose of self-injected 40 mg adalimumab (tumor necrosis factor-α [TNF-α] inhibitor) fortnightly for 3 years. This treatment had been well tolerated achieving a favorable remission. Physical examination revealed stable vital signs and palpable purpura on both legs (FIGURE 1A), along with ankle joint edema. Complete blood cell counts showed white blood cells of 8,000/mm^3, hemoglobin of 11.2 g/dl, and platelets of 247,000/mm^3. Biochemical tests showed elevated levels of C-reactive protein (1.92 mg/dL [reference range, <0.14 mg/dl]), erythrocyte sedimentation rate (104 mm/h [2-10 mm/h]), creatinine (1.17 mg/dl [0.65-1.07 mg/dl]), immunoglobulin (Ig) A (1636 mg/dl [93-393 mg/dl]), and D-dimer (28.5 μg/ml [<1 μg/ml]). Tests for anti-nuclear antibody and anti-neutrophil cytoplasmic antibody were negative. Urinalysis revealed proteinuria and microscopic hematuria. A biopsy of the purpura disclosed leukocytoclastic vasculitis of the dermis, consistent with IgA vasculitis (FIGURE 1B, 1C). CD complicated by IgA vasculitis was then diagnosed. A renal biopsy was performed, which showed mesangial proliferative glomerulonephritis (Fig. 1D). Immunofluorescent staining reveled mesangial deposition of IgA and complement 3, further confirming IgA vasculitis with nephritis. Adalimumab was discontinued and intravenous pulse methylprednisolone 1g daily was administrated for 3 days, followed by oral prednisolone 30 mg. IgA vasculitis-related manifestations resolved and prednisolone was tapered. Two years later, another TNF-α inhibitor, infliximab, was administered intravenously to treat CD-related diarrhea with the informed consent. However, palpable purpura reappeared after a routine induction regimen with 300 mg infliximab at week 0, 2, and 6. Infliximab was then ceased and the purpura resolved. He was treated conservatively with additional elemental diet therapy of Elental® [EA Pharma Co., Ltd, Japan], 1,200 kcal daily).

Various types of vasculitis can occur as an extra-intestinal manifestation of inflammatory bowel diseases (IBD) including ulcerative colitis (UC) and CD. A large case series reported that these vasculitis include large-vessel vasculitis, cutaneous vasculitis, and anti-neutrophil cytoplasmic antibody-associated vasculitides [1]. Although TNF-α inhibitors have been widely applied to IBD with dramatic clinical effectiveness, they can induce various adverse effects including vasculitis, thromboembolic events, lupus-like syndrome, and other autoimmune manifestations [2]. There have been several reports of IBD complicated by IgA vasculitis (formerly Henoch-Schönlein purpura) following TNF-α inhibitors, such as infliximab and adalimumab [3-5]. Although the mechanisms of this adverse effect remain unclear, several hypotheses have been suggested to explain this link: deposition of TNF-α inhibitor/TNF-α immune complexes in vessels, direct drug toxicity, autoantibody production, and a shifts from a Th1 to a Th2 profile in T cell responses [2, 4]. A causal link between the drug and adverse effects usually seems to be speculated when a short period exists from the drug initiation to event onset; however, TNF-α inhibitor-related vasculitis can occur over 2 years of administration [2, 5]. We should also be aware of the potential risk of vasculitis relapse induced by the re-challenge with a different TNF-α inhibitor, as in this case. Careful monitor for potential adverse effects is essential.

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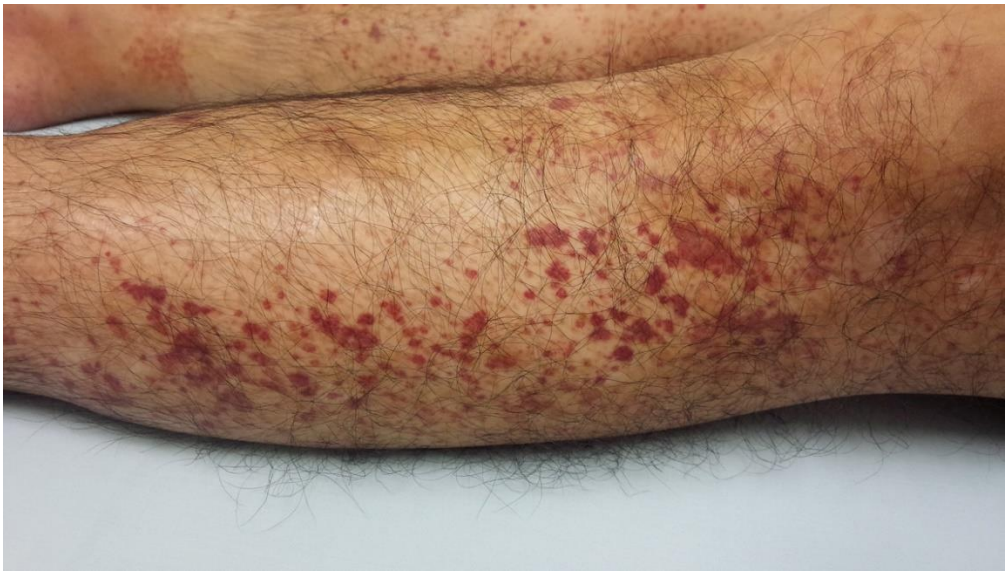

Figure 1A. Palpable purpura on both legs.

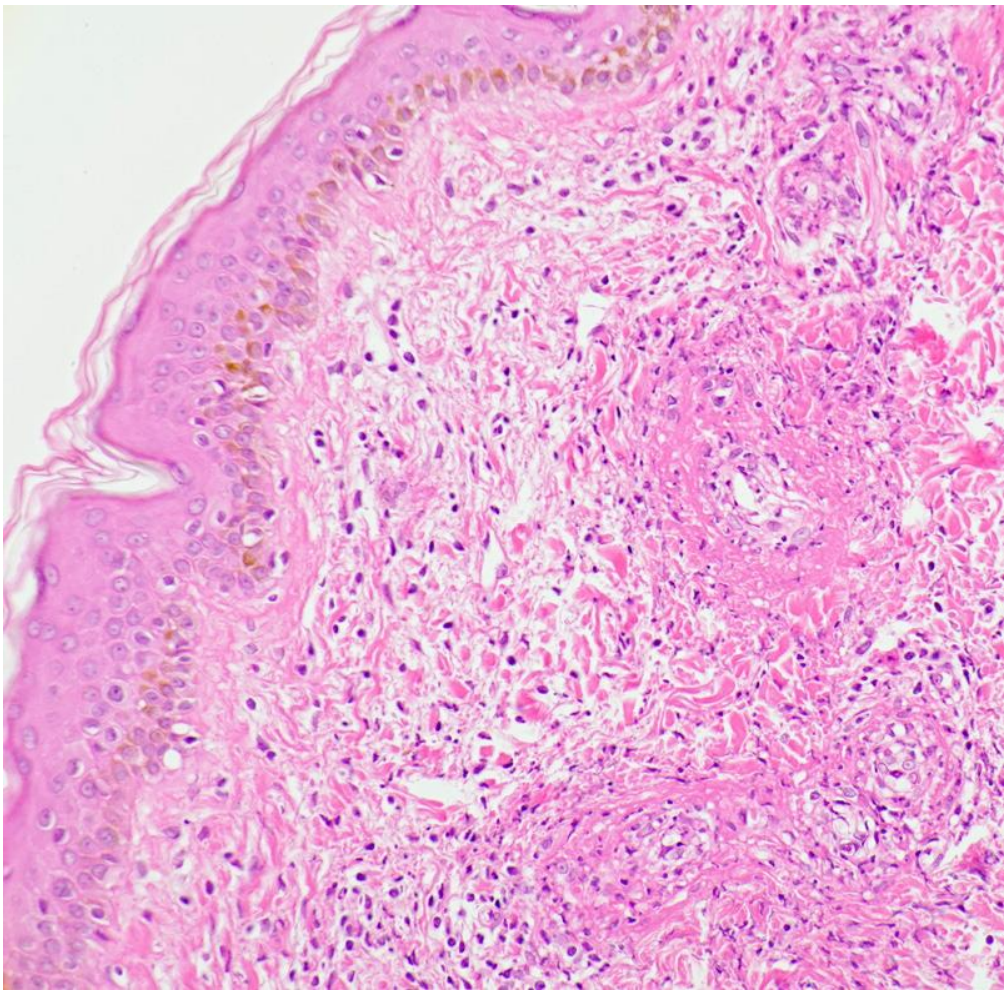

Figure 1B. Biopsy of the purpura revealing leukocytoclastic vasculitis of the dermis (Hematoxylin-eosin staining, × 20).

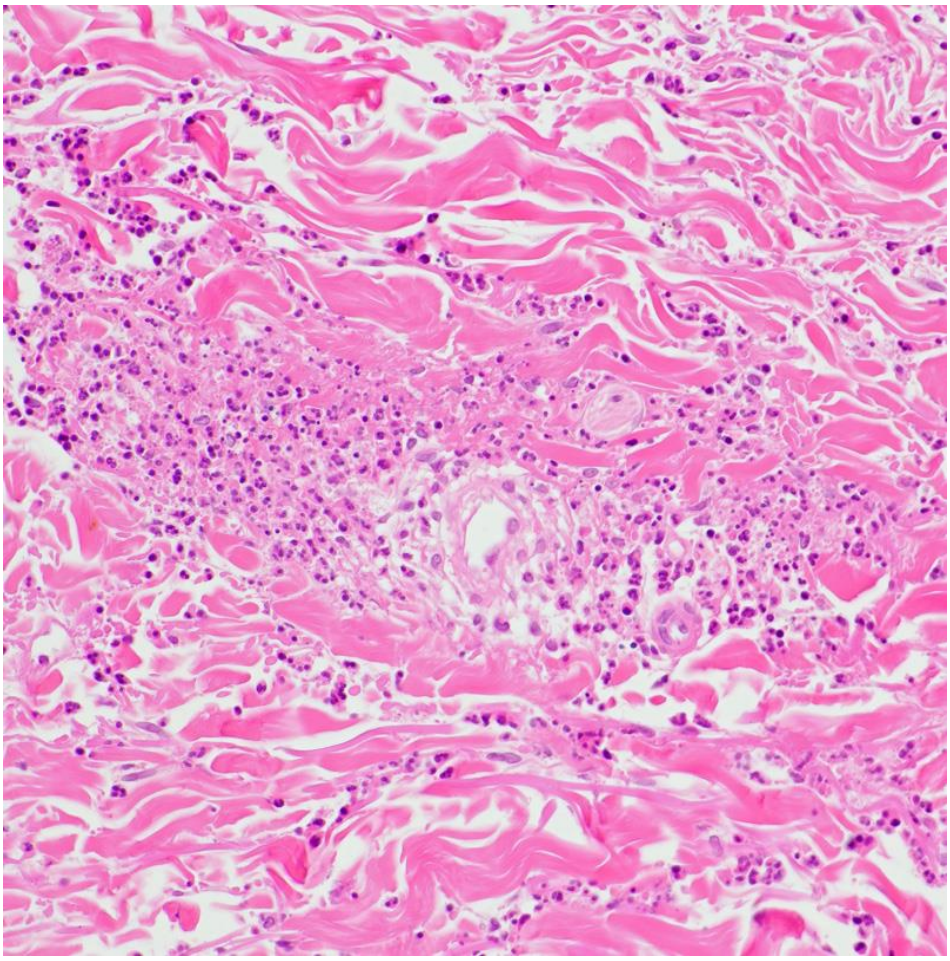

Figure 1C. A high power view disclosing perivascular neutrophilic infiltrate with nuclear dust and focal fibrinoid necrosis (Hematoxylin-eosin staining, × 40).

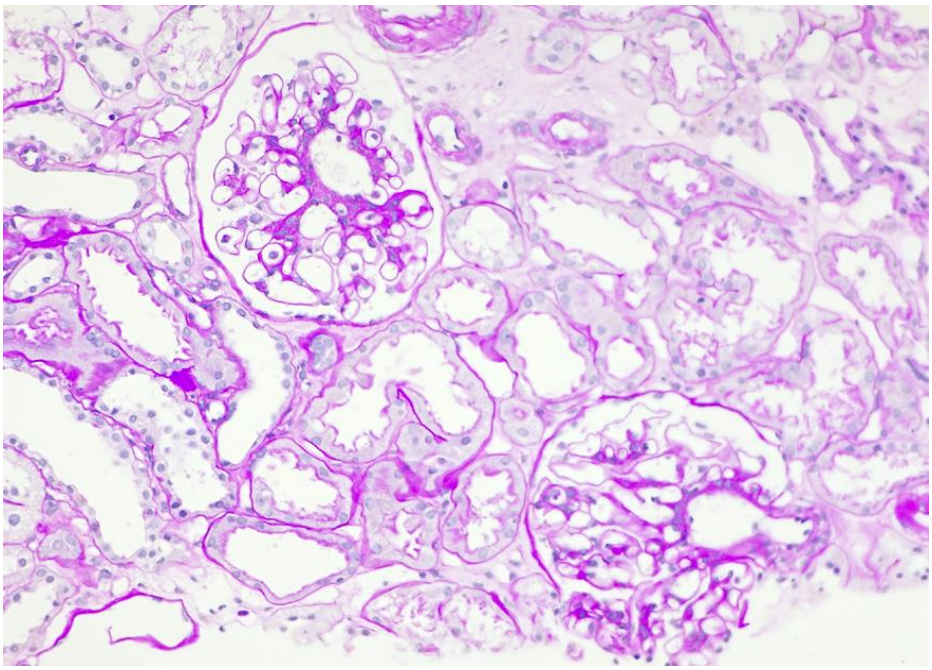

Figure 1D. Renal biopsy showing mesangial focal proliferative glomerulonephritis (Periodic acid-Schiff staining, × 40).